REMARKS

Claims 3 and 12-34 are pending. Claims 12-27 and 29-31 have been withdrawn from consideration as being drawn to non-elected inventions. Claims 3, 28, and 32-34 were rejected under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph. Claims 3 and 32-34 were rejected under 35 U.S.C. § 112, second paragraph. Applicants address these rejections as follows.

Oath and Declaration

As required by the Examiner, enclosed herewith is a new Combined Declaration and Power of Attorney in compliance with 37 C.F.R. § 1.67(a).

Summary of the Invention

In general, the invention is directed to a fusion nucleic acid that includes a first nucleic acid operably linked to a heterologous second nucleic acid, where the first nucleic acid includes any one of the sequences of SEQ ID NOS:1-20, for example, SEQ ID NO:17, and where the mRNA form of the first nucleic acid has RNA binding protein (RBP) binding activity or regulates the functionality of the mRNA form of the fusion nucleic acid.

In the Restriction Requirement mailed on April 9, 2002, the Office states (page 3):

> Claim 32 link(s) inventions of Groups 1-20. The requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claim 32. Upon allowance of the

> linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application.

In response, Applicants elected the invention of Group 17, which is directed to the nucleic acid sequence of SEQ ID NO:17 in their reply to this restriction requirement. However, in view of the Office's statement in the restriction requirement, Applicants submit that claim 32 presently should not be limited to SEQ ID NO:17. Thus, the following arguments also apply to the other nucleic acid sequences to which claim 32 is directed.

Claim Amendments

New claim 35 finds support in original claim 33 and new claims 36 and 37 find support in original claim 32. No new matter has been added by these amendments.

Rejection under 35 U.S.C. § 101 and 35 U.S.C. § 112, First Paragraph

Claims 3, 28, and 32-34 were rejected under 35 U.S.C. § 101 and under 35 U.S.C. § 112, first paragraph, as not being supported by a specific or a substantial asserted utility or a well established utility. In particular, the Office states (page 4):

> The asserted utilities are not specific in that the protein or proteins that apparently bound the RNA comprising SEQ ID NO:17 are not identified in the instant specification. For example, using the claimed nucleic acid hybrid to identify compounds that affect a specific RNA/RBP binding pair

> cannot be considered to be specific in the absence of an identified RBP specific to SEQ ID NO:17. Moreover, the ability of the nucleic acid comprising SEQ ID NO:17 to modify expression of a protein encoded by the fusion transcript in a specific manner (i.e. stabilize, destabilize, sequester, etc.) has not been demonstrated ... Finally, use of the claimed chimeric nucleic acid to identify novel RBP/RNA binding pairs cannot be considered specific because it is not known that the proteins that bound the RNA in the binding assay described in the specification do not also bind other RNAs.

Applicants respectfully disagree as follows.

The sequence of SEQ ID NO:17 is part of the un-translated region (UTR) of a human leptin nucleic acid sequence. The specification, for example, at page 10, line 26, to page 11, line 1, clearly states that this sequence is the human homologue of a gene involved in murine obesity. Moreover, leptin is well known in the art to be an integral component of the physiological mechanism evolved to regulate fuel stores and energy expenditure and, thus, plays a key role in obesity disorders (see, for example, Marti et al., "Leptin: Physiological Action" *J. Physiol. Biochem.* 55:43-49, 1999; copy enclosed). The Revised Interim Utility Guidelines Training Materials (available at http://www.uspto.gov/web/menu/utility.pdf; "The Guidelines") state that a specific utility is a "utility that is specific to the subject matter claimed."

Applicants' specification describes that the taught UTR sequences, including SEQ ID NO:17, have RNA binding protein (RBP) binding activity. In particular, at page 11, lines 20-26, the specification states:

> The binding pair interactions between the UTR sequences of

> the invention and RBP's in the cellular extracts were facilitated by a binding solution containing 7.5 mM Bis-Tris Propane, pH 8.5, 50 mM K^+, 1 mM Mg^{++} 0.2 mM DTT, and 10% (v/v) glycerol. Poly r(G), tRNA, heparin molecules, and unrelated RNA molecules of similar length were used as non-specific competitors of the RNA/RBP binding pair interactions. The interactions were detected by filter binding assay or electrophoretic gel mobility shift assay. (Emphasis added)

Accordingly, Applicants demonstrated that RBPs bound specifically to the claimed UTR sequences. Applicants' specification also teaches that (page 19, lines 5-8):

> RNA molecules comprised of the disclosed parent nucleic acid sequences, or their optimized subfragments, can be used in screening procedures to identify compounds that affect the RNA/RBP binding pair interaction associated with these RNA molecules. (Emphasis added)

And at page 8, line 23, to page 9, line 2 teaches that:

> A compound identified in these screens as having an effect on a particular RNA/RBP binding pair interaction, or on the mRNA functionality, can modulate the expression of a gene product that is endogenously associated with the RNA sequence screened. Therefore, such compounds can be administered as a therapeutic for diseases associated with this protein.

Clearly, Applicants assert that the claimed nucleic acid sequences may be used in a screening method to identify a therapeutic compound, and, thereby, assert a utility for these nucleic acid sequences. Furthermore, the sequence of SEQ ID NO:17 is a part of the UTR of a human leptin, and leptin is involved in a variety of human diseases, such as obesity. Consequently, one skilled in the art would recognize the utility of such a method

for identifying compounds that affect the stability of expression of a leptin nucleic acid sequence, and that such compounds may be used to treat human disease.

The Office also states (page 4):

> The asserted utilities are not substantial in that for each of the asserted activities, it would require further experimentation in order to confirm a specific utility. For example, it would require further experimentation to determine the nature and number of different proteins responsible for binding the RNA comprising SEQ ID NO:17 in the binding assay described in the specification.

With regard to substantial utility, the Guidelines state (page 6):

> [Substantial utility is] a utility that defines a "real world" use ... An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. (Emphasis added)

The use of the nucleic acid sequence recited in the present claims for identifying proteins that interact with this sequence satisfies the substantial utility requirement as exemplified in the Guidelines. Leptins are known in the art to be involved in disease. Applicants' specification shows that RBPs from an extract obtained from cells normally expressing leptins bind the sequence of SEQ ID NO:17. Applicants further show that this binding is specific by adding competing RNAs to the binding reaction and detecting the interaction by using methods standard in the art. No further experimentation is required to show that the presently claimed sequence binds to proteins that are likely to affect leptin stability or expression. In addition, as is stated in Dr. Anthony Giordano's Declaration under 37

C.F.R. § 1.132 submitted with the Continued Prosecution Application filed on January 28, 2002, UTRs are expected to maintain their regulatory function when operably linked to a heterologous sequence, such as a reporter gene. Applicants' disclosure therefore provides a "real world" context of use in identifying potential candidate compounds for preventive measures or further monitoring.

Moreover, the M.P.E.P. sets forth (§ 2107 III (B)):

> Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong" ... Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic of the underlying assertion.

In addition, the Federal Circuit, in *In re Brana*, 34 U.S.P.Q.2d 1436, 51 F.3d 1560 (Fed Cir. 1995), has articulated the standard to be applied by the U.S. Patent Office in any challenge to an assertion of utility. In this case, the court stated (page 1566):

> [T]he PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. [citation omitted] Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.

The Office has failed to show that the asserted utility of the present invention is not credible. As is noted above, the present invention describes the UTR sequences

disclosed in the specification, including SEQ ID NO:17, may be used in a screening assay to identify proteins that bind to these sequences. As is stated in the specification, for example, at page 2, line 24, to page 3, line 6, and page 8, line 26, to page 9, line 1, proteins that bind such a nucleic acid sequence may be used as therapeutics to treat a human disease, e.g., an obesity-related disorder.

This asserted utility is credible as Applicants have shown that proteins bind to these nucleic acid sequences in the presence of competing, non-specific RNAs. With respect to SEQ ID NO:17, Applicants submit that the function of leptin is well known in the art and one skilled in the art would reasonably expect a compound that binds a leptin nucleic acid sequence to affect the stability of a leptin nucleic acid sequence or the expression of a protein encoded by a leptin nucleic acid sequence and, therefore, affect a biological activity of leptin. As leptin has been shown to play a role in disease, such compounds have a specific, substantial, and credible utility. In view of the above arguments, the presently claimed invention meets the utility requirements of 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph. The utility rejection of claims 3, 28, and 32-34 may be withdrawn.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 3, 28, and 32-34 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not adequately described in the specification. In

particular, the Office states (page 6, page 7):

> Regulating functionality can comprise an alteration in pre-mRNA processing or in the stabilization, translation efficiency, localization, sequestration, editing or splicing functions. Thus, the rejected claims embrace a number of different possible effects of SEQ ID NO: 17 on a chimeric transcript comprising SEQ ID NO: 17.
>
> * * *
>
> Given that the claimed invention comprises a critical element of regulating mRNA functionality that embraces several different processes ... and given that the lack of a structural/functional basis in the instant specification or prior art to envision the actual effect of SEQ ID NO: 17 on a transcript comprising SEQ ID NO: 17, one of skill in the art would not be able to reliably envision the claimed invention. Therefore, one of skill in the art would reasonably conclude that applicants were not in possession of the claimed invention.

Applicants submit that the presently claimed invention was adequately described in the original specification. For example, at page 9, lines 2-8, Applicants state:

> We discovered certain nucleic acid sequences, derived from mRNA untranslated regions (UTRs) of a variety of therapeutically-relevant genes, that specifically bind RNA binding proteins (RBPs) (SEQ ID Nos 1-20). We have also discovered methods of subdividing such RBP-binding nucleic acid sequences (parent sequences) to obtain shorter nucleic acid sequences that maintain an RNA/RBP binding pair interaction or mRNA functionality that is equivalent to the parent sequences. (Emphasis added)

Moreover, as is noted above, Applicants demonstrated the RBP binding activity of the UTR sequences in the presence of Poly r(G), tRNA, heparin, and unrelated RNA molecules of similar length. The interactions were detected using a filter binding assay or

an electrophoretic gel mobility assay. Clearly, in their specification, Applicants describe the UTR sequences as being able to specifically bind proteins, exactly as claimed in claim 32.

Furthermore, one skilled in the art would reasonably expect a protein that specifically binds to the claimed UTR sequence to affect the functionality of the mRNA form of a fusion nucleic acid including this UTR sequence. Applicants submit that, to satisfy the written description requirement, one need only communicate to those skilled in the art that the claimed subject matter is intended to be part of their invention. The M.P.E.P. (§ 2163.02; Eighth Edition, August 2001) states:

> An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she has invented what is claimed."

To satisfy this standard, the Federal Circuit has held that the specification need only convey with reasonable clarity to a skilled artisan that the inventor "was in possession of the invention" at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In addition, in *Lilly*, the Federal Circuit acknowledged that "every species in a genus need not be described in order that a genus meets the written description requirement." *Regents of the Univ. of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997) (citing *Utter v. Hiraga*, 845 F.2d 993, 6 U.S.P.Q.2d 1709 (Fed. Cir. 1988)) ("A specification may, within the meaning of § 112, ¶ 1, contain a written description of broadly claimed invention without describing

all species that claim encompasses.")

Applicants' specification plainly meets the written description standard by teaching that RNA binding proteins specifically bind to the claimed UTR sequences. The written description standard does not require Applicants to disclose every possible protein that can bind the claimed UTR sequence nor does it require Applicants to state how each protein that binds a UTR sequence affects the fusion nucleic acid.

Applicants describe, for example, at page 5, line 26, to page 6, line 5, that mRNA functionality may involve an alteration in pre-mRNA processing or in stabilization, translational efficiency, localization, sequestration, editing, or splicing functions of an mRNA. Assays for determining such functionality are standard in the art and are described, for example, at page 7, lines 8-21, of Applicants' specification.

Moreover, Applicants have, from the time they filed this application, claimed the described fusion nucleic acid as part of their invention. One skilled in the art would therefore certainly recognize that, at the time of filing, the inventors were in possession of the claimed isolated fusion nucleic acids. Applicants submit that the 35 U.S.C. § 112, first paragraph, rejection may be withdrawn.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 3 and 32-34 were rejected under 35 U.S.C. § 112, second paragraph, for being directed to non-elected embodiments of the invention and claim 33 is rejected for

containing both a broad limitation and a narrow limitation that falls within the broad limitation. Applicants address these rejections as follows.

As is noted above, the Office stated, in the Restriction Requirement mailed on April 9, 2002, that claim 32 links the inventions of Groups 1-20, and that:

> The requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claim 32. Upon allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application.

In view of this statement, Applicants submit that, while the invention of Group 17 is presently being examined, claim 32 does not need to be amended to be directed to the elected invention at this time. This rejection of claims 3, and 32-34 may be withdrawn.

In addition, Applicants amend claim 33 to be directed to a fusion nucleic acid that is DNA and add new claim 35 which is directed to the fusion nucleic acid of claim 33, where the DNA is cDNA. In view of these amendments, the 35 U.S.C. § 112, second paragraph, rejection of claim 33 may be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance and such action is respectfully requested.

Applicants note that the Office Action was mailed to the incorrect address. Effective immediately, please address all communication in this application to:

Kristina Bieker-Brady, Ph.D.
Clark & Elbing LLP
101 Federal Street
Boston, MA 02110

Enclosed is a "marked-up" and a clean version of the amended claims. Also enclosed is a Petition to extend the period for replying to the Office Action for three months, to and including February 23, 2003, and a check in the amount of $465.00 in payment of the required extension fee. Further, enclosed is a check in the amount of $27.00 in payment of excess claims fees for three excess dependent claims added.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: February 20, 2003

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3. (Twice Amended) The isolated fusion nucleic acid sequence of claim 37, wherein the regulation of mRNA functionality comprises an alteration in pre-mRNA processing or in the stabilization, translational efficiency, localization, sequestration, editing, or splicing function of said mRNA form of said fusion nucleic acid.

28. (Twice Amended) The isolated fusion nucleic acid of claim 32, wherein the nucleotide sequence of said first nucleic acid comprises SEQ ID NO:17.

32. An isolated fusion nucleic acid, comprising a first nucleic acid operably linked to a heterologous second nucleic acid, wherein said first nucleic acid comprises any one of SEQ ID NOS: 1-20, and wherein the mRNA form of said first nucleic acid has RNA binding protein (RBP) binding activity or regulates the functionality of the mRNA form of said fusion nucleic acid.

33. (Amended) The isolated fusion nucleic acid of claim 32, wherein said fusion nucleic acid is DNA.

34. The isolated fusion nucleic acid of claim 32, wherein said fusion nucleic acid is mRNA.

35. (New) The isolated fusion nucleic acid of claim 33, wherein said DNA is cDNA.

36. (New) The isolated fusion nucleic acid of claim 32, wherein said first nucleic acid has RNA binding protein (RBP) binding activity.

37. (New) The isolated fusion nucleic acid of claim 32, wherein said first nucleic acid regulates the functionality of the mRNA form of said fusion nucleic acid.

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Version of Claims Showing Changes Made

Amend claims 3, 28, and 33 as follows.

3. (Twice Amended) The isolated fusion nucleic acid sequence of claim [32] 37, wherein the regulation of mRNA functionality comprises an alteration in pre-mRNA processing or in the stabilization, translational efficiency, localization, sequestration, editing, or splicing [functions] function of said mRNA form of said fusion nucleic acid.

28. (Twice Amended) The isolated fusion nucleic acid of claim 32, wherein the nucleotide sequence of said first nucleic acid comprises SEQ ID NO:17.

33. (Amended) The isolated fusion nucleic acid of claim 32, wherein said fusion nucleic acid is DNA [or cDNA].

Add new claims 35-37.

--35. (New) The isolated fusion nucleic acid of claim 33, wherein said DNA is cDNA.

36. (New) The isolated fusion nucleic acid of claim 32, wherein said first nucleic acid has RNA binding protein (RBP) binding activity.

37. (New) The isolated fusion nucleic acid of claim 32, wherein said first nucleic acid regulates the functionality of the mRNA form of said fusion nucleic acid.--